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Case Report

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Relapsing severe anaemia due to primary parvovirus B19 infection after renal transplantation: a case report and review of the literature

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Introduction

In renal transplant recipients Parvovirus B19 (PB19) infection can lead to severe anaemia, due to lytical replication within erythroid progenitor cells. Clearance of PB19-infection and protective immunity is assumed to be provided by specific PB19-IgG-antibodies [1]. In fact, passive transfer of PB19-IgG-antibodies by means of intravenous immunoglobulin (IvIg) preparations is successfully used to treat PB19-related anaemia [1,2]; however, several reports have shown that PB19-related anaemia can recur despite treatment with IvIg [2–11].

In this report we describe in detail a renal transplant patient who experienced relapsing severe PB19-related anaemia and we reviewed the current literature regarding factors associated with relapsing disease. Our data suggest that primary PB19-infection after kidney transplantation and polyclonal T-cell depleting therapies are risk factors for relapsing PB19-related anaemia. In addition, they support the concept that a PB19-specific cellular immune response is critical to control PB19-infection and establish protective immunity.

Case report

The course of haemoglobin/reticulocytes, PB19-serology/PCR, immunosuppression, and therapy for PB19-infection is summarized in Figure 1. This 32-year-old female patient with end-stage renal disease due to Alport's syndrome received a renal transplant from her father. Initial immunosuppression consisted of tacrolimus, mycophenolate-mofetil, prednisone and basiliximab, given on days 0 and 4. On day 4 post-transplant, she experienced antibody-mediated rejection, which was successfully treated with high-dose steroids and a polyclonal anti-T-lymphocyte globulin (ATG). Subsequently, the patient developed anaemia, which was assumed to be related to ATG and four blood transfusions were given [12]. However, haemoglobin dropped again to 68 g/l with marked reticulocytopenia (10×10^9/l, normal range $40–140 \times 10^9$/l).

Further investigations revealed a positive PB19-PCR in serum (log 6.8 copies/ml), weak positive PB19-IgM-antibodies (1.5; positive >1.0) and PB19-IgG-antibodies (1.9; positive >1.0). Retrospectively, the recipient had negative PB19-IgG-antibodies (<0.8) and PB19-PCR pre-transplant. The kidney donor had negative PB19-PCR, negative PB19-IgM (<0.8) but positive PB19-IgG-antibodies (1.9), consistent with immunity to PB19 without viraemia. Furthermore, all blood transfusions the patient had received were tested negative by PB19-PCR. Therefore, our patient had community-acquired primary PB19-infection.

After therapy with IvIg (cumulative dose 150 g) a prominent increase in reticulocyte counts was observed and anaemia resolved, while PB19-viraemia persisted despite high levels of PB19-IgG-antibodies passively transferred through IvIg. Three and a half months after treatment with IvIg, anaemia with reticulocytopenia recurred and two blood transfusions were given. At this time point PB19-viraemia was log 7.0 copies/ml and PB19-IgG-antibodies became negative again. Bone marrow biopsy confirmed the diagnosis of relapsing PB19-infection by the presence of giant proerythroblasts and a positive PB19-PCR. A second course of IvIg (cumulative dose 125 g) was given, which was again followed by an increase of reticulocyte counts and resolution of anaemia.

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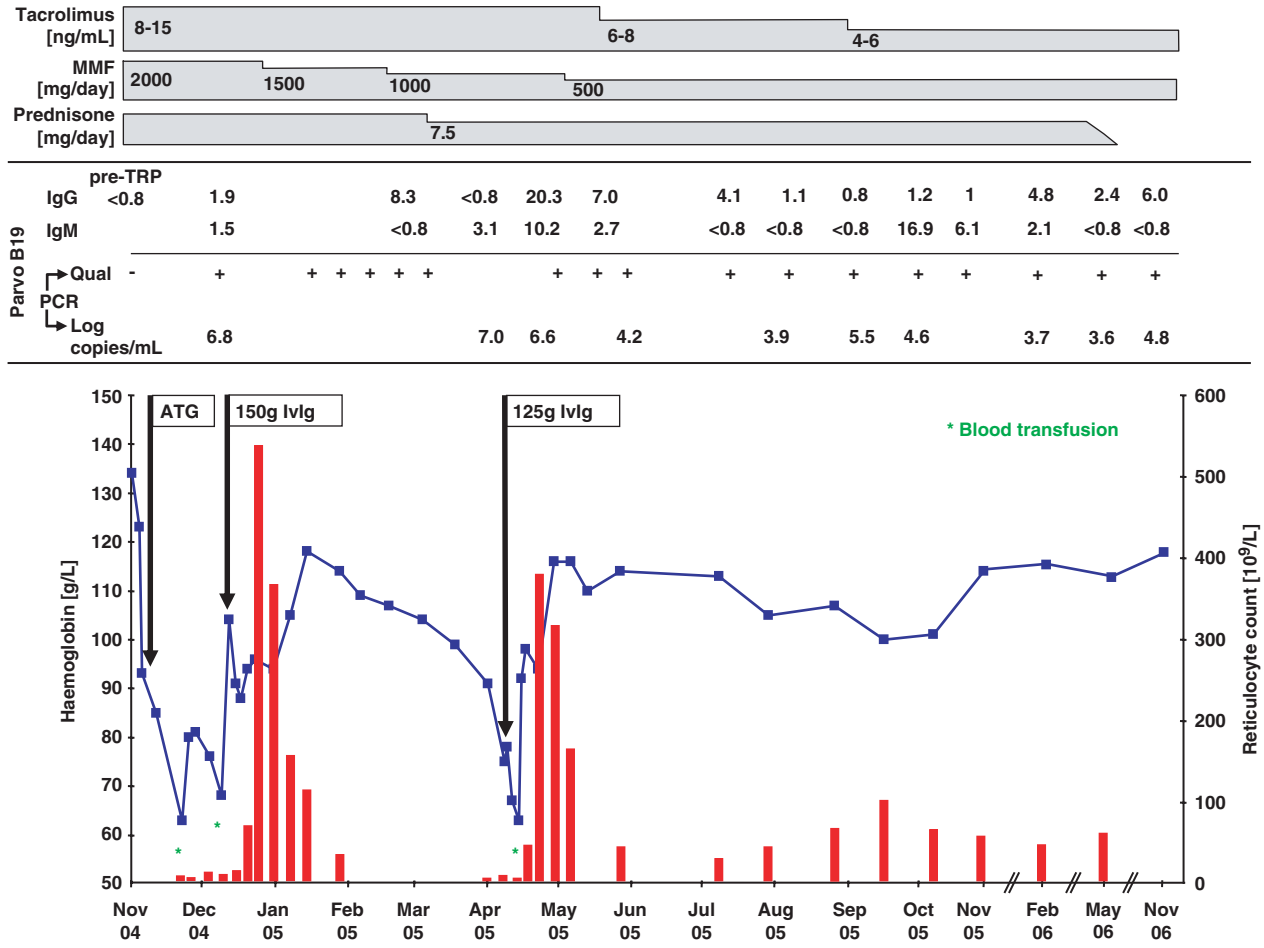

Fig. 1. Immunosuppression and therapy with intravenous immunoglobulin (IvIg), Parvovirus B19 (PB19)-serology and viraemia, haemoglobin and reticulocyte counts from November 2004 to November 2006. PB19-serology was performed by use of the PB19-IgG/IgM-EIA (Denka Seiken). PB19-IgM-antibodies >1.0 and PB19-IgG-antibodies >1.0 are considered positive. Qualitative and quantitative real-time PB19-PCR was performed as described previously [15]. Normal reticulocyte counts range from 40 to 140 × 10^9/l. ATG, polyclonal anti-T-lymphocyte globulin; MMF, mycophenolate-mofetil.

Concurrently, baseline immunosuppression was further reduced (tacrolimus trough levels from 8–15 ng/ml to 6–8 ng/ml, mycophenolate-mofetil dose from 1 g/day to 0.5 g/day).

Within the next 18 months, anaemia did not recur and reticulocyte counts were mostly in the normal range. PB19-IgG-antibody levels again became negative 4 months after the second IvIg course. Thereafter, PB19-IgG-antibody levels continuously increased with transient high levels of PB19-IgM-antibodies consistent with recipient-derived production. However, despite considerable levels of PB19-IgG-antibody levels over 9 months (February 2006 to November 2006), PB19-viraemia persisted between log 3.6 and 4.8 copies/ml under dual immunosuppression consisting of tacrolimus (trough levels to 4–6 ng/ml) and mycophenolate-mofetil (0.5 g/day).

Renal allograft function recovered after the early rejection episode and remained stable during the 2-year follow-up, with an actual serum creatinine of 132 µmol/ml (estimated glomerular filtration rate 51 ml/ml) and no proteinuria.

Review of the literature

Medline search between 1986 and 2006 yielded 49 kidney transplant recipients with PB19-related anaemia and follow-up data on relapsing disease (Supplementary table 1). We extracted data on primary PB19-infection, baseline immunosuppression, induction therapy, therapy of first PB19-related anaemia episode, clinical response to therapy (i.e. haemoglobin recovery), virological response to therapy (i.e. clearance of PB19-viraemia), relapse of PB19-related anaemia and therapy of second PB19-related anaemia episode. Overall, the percentage of missing data was substantial (primary PB19-infection: 73%, baseline immunosuppression: 33%, induction therapy: 35%, therapy of first PB19-related anaemia episode: 10%, clinical response to therapy (i.e. haemoglobin recovery): 16%, virological response to therapy (i.e. clearance of PB19-viraemia): 67%) limiting the validity of the following analysis.

Relapsing PB19-related anaemia was observed in 16/49 patients (33%). Thirty-nine of 44 patients (89%)

with recorded therapy for the first PB19-related anaemia episode received IvIg, while in four patients only, baseline immunosuppression was reduced (i.e. azathioprine or mycophenolate-mofetil). Relapsing anaemia was observed more often in patients with primary PB19-infection (8/13 patients (62%) *vs* 8/36 patients (22%); $P = 0.02$). Data on induction therapy was recorded in 32/49 patients (65%). Nineteen of 32 patients (59%) received no induction therapy, while 13 patients had different induction agents [ATG ($n = 7$), ALG ($n = 2$), IL-2 receptor blockers ($n = 3$), OKT3 ($n = 1$)]. Relapsing anaemia was observed more often in patients having received ATG [ATG: 6/7 patients (86%); other induction agents: 2/6 patients (33%); no induction: 6/19 patients (32%); $P = 0.04$]. There were no significant associations between relapsing PB19-related anaemia and baseline immunosuppression ($P = 0.17$) therapy of first PB19-related anaemia episode ($P = 0.28$), clinical response to therapy ($P = 0.32$) and virological response to therapy ($P = 0.98$).

Discussion

IvIg is widely used to treat PB19-related anaemia because it contains high amounts of neutralizing PB19-IgG-antibodies [1,2]. Indeed, the humoral immune response is regarded as the major mechanism responsible for clearance of PB19-infection [13]. Our case demonstrates that treatment with IvIg is in fact followed by a marked increase of reticulocyte counts and a reduction of PB19-viraemia. However, these passively transferred antibodies were unable to control PB19-infection. This observation suggests that PB19 persists in the intracellular compartment (e.g. erythroid progenitor cells), which is not accessible to antibodies, and that a PB19-specific cellular immune response is required to control and clear the infection. In this context, longitudinal analysis of PB19-specific CD4 and CD8 T-cells would have been of particular interest in the reported case, but were not available [14].

Nevertheless, there is indirect evidence that T-cells are of critical importance to control and clear PB19-infection. First, relapse of PB19-related anaemia was common (16/49 patients; 33%) despite treatment with IvIg and relapsing disease was associated with T-cell depleting therapy (i.e. ATG). Second, our case and several other reports indicate that PB19-infection was better controlled after reduction of therapies suppressing preferably T-cells (e.g. calcineurin-inhibitors) [7,8,10]. Third, Isa *et al* [14]. found a high frequency of activated PB19-specific CD8 T-cells beyond the first year after infection, despite resolution of clinical symptoms and control of viraemia in healthy individuals. This long-lasting CD8 T-cells response indicates a significant function of the cellular immune response to control and possibly clear PB19-infection. Indeed, the observed enduring activated CD8 T-cell response may be due to persistence of low amounts of PB19 in intracellular compartments (e.g. in erythroid progenitor cells). However, it is as yet unknown whether PB19 is completely cleared from the human host or whether true latency exists, as known for many viruses (e.g. herpesvirus family, polyomavirus BK) [14].

Our observation may also have implications for clinical management of patients with PB19-related anaemia. Patients with primary PB19-infection and/or therapies with T-cell depleting antibodies are at increased risk for relapsing disease. Therefore, such patients should be closely monitored when the protective effect of IvIg vanishes about 3 months after therapy. Furthermore, baseline immunosuppression should be carefully lowered to improve the potential of the immune systems to mount a sufficient response to control PB19-infection.

In conclusion, primary PB19-infection and polyclonal T-cell depletion therapies are risk factors for relapsing severe PB19-related anaemia, which may require repetitive treatments with IvIg. In addition, our data suggest that development of a PB19-specific cellular immune response is essential to control PB19-infection and establish protective immunity.

Supplementary material

For Supplementary Material, please refer to NDT Online

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Conflict of interest statement. None declared.

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